# CLINICAL TRIAL AGREEMENT BETWEEN Collaborator AND THE CENTER FOR CANCER RESEARCH, NATIONAL CANCER INSTITUTE, FOR THE CLINICAL DEVELOPMENT OF Agent

## INTRODUCTION

The Center for Cancer Research (CCR), National Cancer Institute (NCI), recognizes the importance of the pharmaceutical industry in the clinical development of new cancer treatment, prevention and control agents. CCR wishes to foster collaboration with industry wherever possible. As part of its mission to improve cancer care, CCR shares with industry the important goal of defining the contribution of a new drug or biologic in the treatment, prevention and control of cancer. CCR therefore recognizes and supports the need of a private sponsor to focus at the appropriate time on clinical trials which lead to a New Drug Application (NDA) and a Biological License Application (BLA), since an NDA and a BLA are the vehicles through which new cancer treatment, prevention and control therapies become widely available to cancer patients and the public. Thus CCR considers it appropriate to do clinical trials of interest to, and partially supported by, a pharmaceutical firm, provided that the trials have scientific merit and are consistent with the overall goals of the CCR.

Inasmuch as CCR coordinates a large volume of clinical research with new cancer treatment, prevention and control agents, industry recognizes CCR's need to be aware of industry's plans for the clinical development of new agents of mutual interest, particularly if a pharmaceutical firm wishes to utilize the resources of the CCR. Industry also recognizes the necessity of preserving the spirit of free and open inquiry among clinical investigators.

## AGREEMENT

The following statement serves as the basis for the codevelopment of Agent for XXX by Collaborator and the CCR.

### 1. DEFINITIONS.

**"Adverse Drug Experience"** means an adverse clinical experience as defined under 21 CFR § 310.305 "Records and Reports Concerning Adverse Drug Experience", and other applicable Federal Regulations. It must be reported immediately to the drug sponsor. [If Collaborator holds the IND, CCR will also report Adverse Drug Experiences directly to the FDA]. "Other" adverse drug reactions are reported if that effect has not been described previously. Specific guidelines and policies for reporting adverse drug reactions, as well as common toxicity criteria have been developed.

**"Affiliates"** means any corporation or other business entity controlled by, controlling, or under common control with Collaborator. For this purpose, "control" means direct or indirect beneficial ownership of at least fifty (50) percent of the voting stock, or at least fifty (50) percent interest in the income of such corporation or other business.

**"Agent"** means XXXXXXXX.

**"Amendment"** means any formal written change to this Clinical Trial Agreement that is made after its effective date in accordance with Paragraph 23 of this Clinical Trial Agreement.

**"Annual Report"** means a brief report of the progress of an IND associated investigation which the IND sponsor is required to submit to the FDA within 60 days of the anniversary date that the IND went into effect (pursuant to 21 C.F.R. § 312.33). If NCI is the drug sponsor, NCI shall provide Collaborator a copy of the Annual Report simultaneously with the submission of the Annual Report to the FDA. [In accordance with CCR procedures, Annual Reports will not be made public.]

**"Biological Product"** means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man, as further defined at 21 C.F.R. § 600.3(h).

"**BLA**" means a Biological License Application. The BLA is a formal process by which the FDA approves a biologic for commercial distribution.

**"Clinical Brochure"** means a document containing all the relevant information about the drug, including animal screening, preclinical toxicology, and detailed pharmaceutical data. Also included, if available is a summary of current knowledge about pharmacology and mechanism of action and a full description of the clinical toxicities.

**"Collaborator"** means _____, a corporation organized and existing under the laws of the State of____, having a place of business at _____ and its Affiliates.

**"Cooperative Research and Development Agreement"** or **"CRADA"** means a joint agreement entered into by NCI and another party pursuant to the Federal Technology Transfer Act of 1986 and Executive Order 12591 of October 10, 1987, as amended by the National Technology transfer and Advancement Act of 1995.

**"CTA"** means Clinical Trial Agreement.

**"CCR"** means the Center for Cancer Research, NCI.

**"DHHS"** means the Department of Health and Human Services.

**"Drug Master Files"** or **"(DMFs)"** means reference files submitted to FDA that are used in the review of investigational and marketing applications for human drugs. Drug Master Files are submitted to the FDA to allow another party to reference this material without disclosing to that party the contents of the file.

**"Drug Product"** means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an Active Ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo, as defined in 21 C.F.R. § 210.3(a)(4). An Active Ingredient means any component that is intended to furnish pharmacological activity or other mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. This term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect, as defined in 21 C.F.R.§ 210.3(a)(7).

**"FDA"** means the Food and Drug Administration, DHHS.

**"Funding Agreement"** means an agreement entered into between a Federal agency and another party for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government.

**"Government"** means the U.S. Government and any of its agencies.

**"Human Subjects"** means individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations for the protection of human subjects, human subjects are defined as living individuals about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information (45 CFR §46.102(f)).

**"IND"** means an Investigational New Drug Application. The IND is the legal mechanism under which experimental drug research is performed in the United States. An IND is submitted to the Food and Drug Administration to receive approval to conduct experimental clinical trials. The FDA regulations require continual updates to the IND including, but not limited to, Annual Reports, adverse drug reaction reports, new protocols, protocol amendments and pharmaceutical data.

**"Investigator"** means any physician who assumes full responsibility for the treatment and evaluation of patients on research protocols as well as the integrity of the research data.

**“IRB”** means the CCR Institutional Review Board

**“Multi-Party Data”** means clinical data which is collected from a clinical study for a combination of proprietary investigational agents supplied by more than one collaborator.

**"NCI"** means the National Cancer Institute, NIH, DHHS.

**"NDA"** means a New Drug Application. The NDA is the formal process by which the FDA approves a drug product for commercial distribution.

**"NIH"** means the National Institutes of Health, PHS, DHHS.

**"Parties"** means Collaborator and NCI.

**"PHS"** or **"USPHS"** means the Public Health Service, DHHS.

**"Principal Investigator"** means a physician who has organizational and fiscal responsibility for the use of federal funds to conduct a plan of research.

**"Proprietary Data"** means confidential scientific, business or financial data, provided that such data:

is not publicly known or available from other sources who are not under a confidentiality obligation to the source of the information;

has not been made available by its owners to others without a confidentiality obligation;

is not already known by or available to the receiving Party without a confidentiality obligation;

does not relate to potential hazards or cautionary warnings associated with the production, handling or use of the subject matter of this Agreement; and

If any one or more of the above provisions of this definition is not met, the relevant information shall no longer be considered proprietary information.

**“Protocol”** means

**"Raw Data"** means the primary quantitative and empirical data first collected by the intramural investigator from experiments and clinical trials conducted under the scope of this Agreement.

**"Sponsor"** means an organization or individual who assumes legal responsibility for supervising or overseeing clinical trials with investigational drugs.

**"Summary Data"** means a summary of the Raw Data which will be made available to Collaborator which summary is used by Collaborator to prepare an Annual Report to the FDA.

## 2. PLANNING OF CLINICAL TRIALS.

When there is a private sponsor, if the drug to be developed is also of interest to CCR, then the overall plan for its clinical development shall be a collaborative undertaking by Collaborator and the CCR; such a plan shall be formulated and/or discussed in joint meeting(s) before implementation of clinical testing. In addition to areas of mutual interest, CCR and Collaborator may independently pursue clinical studies of particular interest to each. Because such independently sponsored studies have implications for commitment of resources by both CCR and Collaborator, they shall also be the subject of joint discussion and planning between the CCR and Collaborator. There should be frequent and full interchange between staff members of the CCR and Collaborator. Furthermore, whenever possible, the planning of a particular trial should be a joint effort of the investigators, Collaborator, and CCR. Notwithstanding the foregoing, neither Collaborator nor CCR shall be required to agree upon an overall plan for clinical development or any other matter if either believes in its sole discretion that to do so would not be in its best interests. With the exception of Agent to be supplied by Collaborator, CCR shall conduct the Phase II clinical trial at its own expense.

## 3. INDs.

Collaborator shall submit an IND for this Study to the FDA. As a general rule, all information in INDs will be fully shared between the CCR and Collaborator as outlined below. However, certain Collaborator proprietary information that is not required for the conduct of the study may be held in confidence by Collaborator and not disclosed to CCR.

## 4. PROTOCOLS.

The protocol, entitled “XXX,” was reviewed by the NCI Institutional Review Board (IRB) on XXXX and was approved pending stipulated changes.

## 5. ADVERSE DRUG EXPERIENCES, ANNUAL REPORTS, OTHER IND DATA.

The CCR will report to Collaborator all adverse drug experiences concurrently with their submission to the FDA. Copies of any warning letters will be sent to CCR by Collaborator when they are sent to participating investigators and to the FDA.

## 6. DRUG INFORMATION AND SUPPLY.

Collaborator agrees to provide to the CCR without charge Agent in sufficient quantity to complete the protocols sponsored by CCR. The contact person for CCR will be XXXXXXX, NCI (Telephone Number (301) 496-XXXX) and the Collaborator contact will be XXXX (Telephone Number XXXX). Furthermore, Collaborator will provide Certificates of Analysis to CCR for each lot of finished product provided.

## 7. DATA RIGHTS.

The data generated in trials conducted by CCR are the property of CCR. Collaborator shall have complete access to all the data and results generated under this Agreement that are in the possession and control of CCR. These data will be made fully available to Collaborator for its own analyses and for its application for FDA approval. If there are additional costs to the investigator for providing such data, the investigator shall be reimbursed for the reasonable additional costs by Collaborator in a manner to be negotiated by investigator and Collaborator after discussing the data required with XXXXXX, (telephone number 301-496-XXXX).

## 8. FDA MEETINGS.

All meetings with the FDA concerning Agent will be discussed by Collaborator and the CCR in advance and will be held on mutually agreed upon dates. Collaborator will have the option to set the agenda for such a meeting. One of the missions of the CCR is to ensure that active investigational prevention and control agents are approved and made widely available in a timely fashion. Therefore, CCR feels it is important to participate in the development plan for Agent and in discussions with the FDA regarding the design and endpoints for pivotal trials. In addition, CCR expects that Collaborator will actively pursue approval of the Agent by FDA and will take the initiative in arranging meetings with the FDA. In the event CCR should meet with FDA to discuss the development of Agent without the presence of a representative(s) from Collaborator, no unpublished data concerning the agent will be discussed with the FDA without Collaborator's permission, excepting safety data.

## 9. PROPRIETARY DATA.

Any preclinical or formulation data considered proprietary by Collaborator will be treated as such by the CCR. Collaborator should state in advance what information it considers proprietary and CCR can accept or decline information so designated. NCI shall treat in confidence any of Collaborator's written information about Study that is stamped "CONFIDENTIAL" for a period of three (3) years from the date of execution of this Agreement, unless Collaborator informs the NCI that the Confidential Information is still secret and confidential, and NCI concurs, in which case the obligations hereof shall extend for a further period of two (2) years. Such Confidential Information shall not include information or data that

was previously known to NCI or that is or becomes publicly available or which is disclosed to NCI without a confidentiality obligation. Primary data relating to sensitive laboratory studies will, upon request by Collaborator, be returned to Collaborator by the CCR. However, summaries of all such studies will be retained in the CCR files.

## 10. DATA MANAGEMENT AND EXCHANGE.

The CCR will supply Collaborator information to be submitted with Collaborator's IND as outlined above, and subject to the limitations set forth in this Agreement. The CCR will receive information from Collaborator's IND including, but not limited to, Annual Reports, Clinical Brochures, adverse drug experiences, and formulation and preclinical data, including toxicology findings.

## 11. MONITORING.

In conjunction with CCR, Collaborator can make arrangements to receive copies of data from CCR's principal investigator in the format Collaborator desires. The Principal Investigator will be reimbursed by Collaborator for the cost of reformatting (if any) and reproduction of the data. Copies of annual data summaries for the CCR monitored study will be available to Collaborator upon request. More frequent monitoring of the CCR monitored study can be arranged. Any arrangement which involves the collection of more than summarized data provided annually will be at the expense of Collaborator. Should the CCR conduct an audit of the study using Agent, Collaborator will be invited to attend and participate in the data review. In addition, should Collaborator choose to review primary medical records at the research site in preparation for an NDA or PLA submission,XXXXX, (telephone number 301-496-XXXX) will provide any assistance necessary to arrange for such a review at Collaborator's expense. Initial contact with the investigator for the purpose of collecting or reviewing data must be approved in advance by CCR.

## 12. PUBLICATIONS.

The CCR investigators maintain the full right to present and publish the data at such time and place as they see fit. Manuscripts should have advisory review and comment by Collaborator a meaningful length of time prior to submission for publication. The amount of time required for the review shall not exceed thirty (30) days. The publication or other disclosure shall be delayed for up to an additional thirty (30) days upon written request by either Party to this Agreement as necessary to preserve U.S. or foreign patent or other Intellectual Property rights. Collaborator may chose to review any manuscript relating to the study prior to its submission. The amount of time required for the review shall not exceed (30) days.

## 13. USE OF NAME and COMMERCIALIZATION.

Collaborator may use, refer to and disseminate reprints of scientific, medical and other published articles which disclose the name of NCI consistent with U.S. copyright laws, provided such use does not constitute an endorsement of any commercial product or service by NCI. Collaborator shall take every step possible to ensure that references to the articles are accurate,

and shall explicitly state that any such reference does not claim, infer or imply an endorsement or recommendation of the product by the Investigator or the U.S. Public Health Service, Department of Health and Human Services. Collaborator shall not use the name of NCI or any of the foregoing in any advertising, packaging, or promotional material in connection with Agent except with the written permission of NCI or as may be required by law.

## 14. PATENTS.

Generally, the rights of ownership of inventions, discovered or made solely in connection with work covered by this Agreement, are retained by the organization that is the employer of the inventor. Both Collaborator and CCR recognize that inventorship will be determined under patent law. When a non-government employee is the sole inventor, the U.S. Government retains a non-exclusive, irrevocable, paid-up license to practice the invention or to have the invention practiced throughout the world by or on behalf of the U.S. Government. NCI will notify Collaborator immediately upon filing a patent application on any invention its employees make while using the Materials furnished to NCI under this Agreement. The NCI will seriously consider Collaborator's request for a nonexclusive, partially exclusive or exclusive royalty-bearing license to make, use and/or sell products embodying the invention as claimed in the filed patent application, subject to the terms of 35 U.S.C. 207, 208, and 209, under 37 CFR Part 404 to any invention made by NCI investigators during this study when a U.S. Government employee is the sole inventor.

## 15. OTHER INTERACTIONS.

In order to foster development of Agent, the participation of CCR and other NIH staff will be required at selected scientific or development meetings. Selection of participating NIH staff must be based on choices mutually acceptable to both Collaborator and NCI. Both Collaborator and NCI must agree that the activities would be appropriate under this Agreement, and acceptance of Collaborator's support of NCI's participation in the activities will be contingent upon appropriate NCI approval. Other interactions which materially assist the development of potentially important new therapies will also be possible. Again, mutual agreement and approval will be necessary, according to the terms of this Agreement. However, notwithstanding anything to the contrary, this agreement does not represent a Cooperative Research and Development Agreement (CRADA under the Federal Technology Transfer Act, 15 U.S.C. 3701 et seq.).

## 16. LIABILITY.

No indemnification for any loss, claim, damage, or liability is intended or provided by any party under this agreement. Each party shall be liable for any loss, claim, damage, or liability that said party incurs as a result of said party's activities under this agreement, except that the NCI, as an agency of the United States, assumes liability only to the extent as provided under the Federal Tort Claims Act (28 U.S.C. Chapter 171).

## 17. GOVERNING LAW.

This Agreement shall be governed by and construed in accordance with Federal law as construed by the Federal Courts of the District of Columbia.

**18. SEVERABILITY.**

The terms of this Agreement are severable. If any item or provision of this Agreement shall to any extent be invalid or unenforceable, the remainder of this Agreement shall not be affected, and each remaining item and provision of this Agreement shall be valid and shall be enforceable to the fullest extent permitted by law.

**19. SURVIVABILITY.**

The provisions of this Agreement as they relate to confidentiality and drug supply shall survive the expiration or earlier termination of this Agreement.

**20. COMPLIANCE WITH DHHS REGULATIONS.**

CCR and Collaborator agree to comply with all appropriate Department of Health and Human Services regulations relating to Human Subject use, and all Public Health Service policies relating to the use and care of laboratory animals.

**21. TERMINATION.**

A. This Agreement expires on the earlier to occur of the completion of the research or five (5) years. Said expiration date may be changed by mutual agreement and written amendment of this Agreement.

B. This Agreement may be terminated at any time by the mutual written consent of the Parties.

C. On expiration or earlier termination of this Agreement, Collaborator will supply enough Agent to complete the clinical studies up through Phase II trials, as are then ongoing, pursuant to the provisions of Paragraph 6.

D. If Collaborator elects to terminate its development of Agent, but CCR elects to continue its development of the drug, the NIH shall have nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any invention which Collaborator may have or obtain on Agent, its manufacture, or on the process for use of Agent, throughout the world, for medical research purposes.

E. If Collaborator elects to terminate its development of Agent for all cancer treatments, but CCR elects to continue its development of Agent, and the Parties have negotiated in good faith the ability of CCR to conduct additional clinical studies pursuant to Paragraph 21D, then Collaborator will continue to allow CCR to purchase, at cost, the Agent in quantities sufficient to supply all said additional clinical studies by either (1) Collaborator allowing CCR to purchase said Agent from Collaborator inventory; or (2) Collaborator arranging for an independent contractor to manufacture and provide for CCR purchase of said Agent. Such obligation of Collaborator shall expire two

years from the date of Collaborator's termination of development of the Agent unless an alternative duration is agreed upon between the Parties at the time of termination.

## 22. CLINICAL TRIAL AGREEMENT AMENDMENTS.

Upon mutual agreement of both parties, this CTA may be amended as necessary to ensure the Agreement accurately reflects the terms and scope of the collaborative research project. The Amendment shall be in writing signed by both the authorized representative of Collaborator and the Director of the CCR.

**Signatures begin on the next page**

## SIGNATURES

This agreement provides the basis for mutually satisfactory codevelopment of AGENT as a cancer prevention and control agent.

By executing this Agreement, each of the undersigned represents and confirms that he is fully authorized to bind his identified company or entity to its terms.

AGREED AND ACCEPTED:

**FOR CCR, NCI**

_____ _____

Director
Center for Cancer Research
National Cancer Institute

Date

9000 Rockville Pike
Building 31, Room 3A11
Bethesda, Maryland 20892

The undersigned expressly certifies or affirms that the contents of any statement made or reflected in this document are truthful and accurate.

**FOR Collaborator**

_____ _____

Name
Title

Date

Mailing Address: